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(54) Title: CRYSTALLINE FORM OF BIS [(E)-7-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL](3R,5S)-3,5-DIHYDROXYHEPT-6 -ENOICACID] CALCIUM SALT

(57) Abstract: Two polymorphic forms of bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6 -enoic acid] calcium salt, processes for making them and their use as HMG Co-A reductase inhibitors are described.

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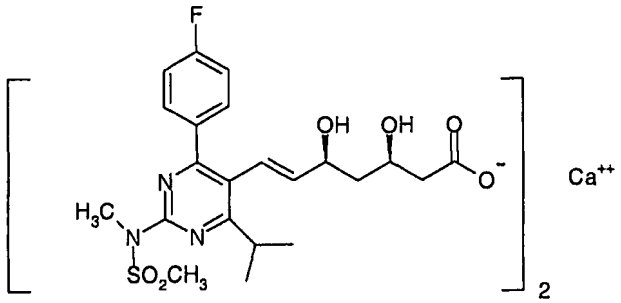
CRYSTALLINE FORM OF BIS [(E)-7-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN-5-YL] (3R, 5S)-3, 5-DIHYDROXYHEPT-6-ENOICACID] CALCIUM SALT

The present invention relates to a novel crystalline chemical compound and more particularly to a novel crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt, hereinafter referred to as "the Agent", and illustrated in Formula (I) hereinafter, which compound is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) and is useful as a pharmaceutical agent, for example in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated. The invention also relates to processes for the manufacture of the crystalline form, pharmaceutical compositions comprising the crystalline form and the use of the crystalline form in medical treatment.



(I)

European Patent Application, Publication No. 521471 (hereinafter EPA 521471), which is herein incorporated by reference, discloses an amorphous (powder) form of the Agent, prepared by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration.

International Patent Application WO 2004/014872 discloses an improved method for the precipitation of the amorphous form of the Agent.

International Patent Application WO 00/42024 discloses a crystalline form of the Agent, referred to as Form A therein, which is prepared from a mixture of water and one or more organic solvents, for example, a 1:1 mixture of acetonitrile and water. However no suitable conditions were found for preparation of Form A from water without the presence of an organic co-solvent. The use of organic solvents in large scale manufacture is generally undesirable for environmental reasons (for example, the disposal of large volumes of waste), and safety reasons (for example, if the product is a pharmaceutical, the need to ensure that

organic solvents are removed from the final product). Therefore there is an on-going need to find crystalline forms of the Agent which can be produced from water alone.

We have now surprisingly and unexpectedly discovered that the Agent can be prepared in a second crystalline form from water without the need for an organic co-solvent.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 8.8, 13.1 and 21.5° (hereinafter referred to as Form B).

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 21.5, 22.8 and 28.9°.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 15.2, 15.8, 17.5, 21.5, 21.9, 22.8, 24.5 and 28.9°.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern substantially as shown in Figure 1.

Form B obtained according to the present invention is substantially free from other crystal and non-crystal forms of the Agent. The term "substantially free from other crystal and non-crystal forms" shall be understood to mean that the desired crystal form contains less than 50%, preferably less than 20%, more preferably less than 10%, more preferably less than 5% of any other forms of the Agent.

The X-ray powder diffraction (referred to herein as XRPD or XRD) spectrum was determined by mounting a sample of the crystalline form on Siemans single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. Using a Siemens D5000 diffractometer, the sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated x-ray source was passed through an automatic variable divergence slit set at V20 (20mm path length) and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 2 hours 6 minutes and 40 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture

was by means of a DECpc LPv 433sx personal computer running with Diffrac AT (Socabim) software.

The X-ray powder diffraction spectra of a typical sample of Form B is shown in Figure 1 hereinafter.

It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample of Form B to another, and so the values quoted are not to be construed as absolute. It will also be understood that the relative intensities of peaks may vary according to the orientation of the sample under test so that the intensities shown in the XRD trace included herein are illustrative and not intended to be used for absolute comparison.

Form B may also be characterised by its infra-red (IR) spectrum, such as that carried out by the DRIFT (Diffuse-Reflectance Infrared Fourier Transform Spectroscopy) technique. A DRIFT spectrum of Form B is shown in Example 1 hereinafter. The spectrum was acquired using 2% w/w (in powdered KBr) over the 4,000 - 400cm-1 spectral range on a Nicolet Magna 860 ESP FT-IR spectrometer. Spectral acquisition conditions were 2cm-1 digital resolution, 64 background scans (KBr only) and 64 sample (2% sample mixed with KBr) scans.

It will be appreciated that the resolution of DRIFT spectra may be influenced by the particle size of the sample being examined. The spectrum for Form B shown hereinafter was obtained with a sample which had been crushed to a fine powder. Repeated samples, or those with an alternative sample preparation may give DRIFT spectra which vary in resolution, although the peak position frequency therein will be unchanged.

Form B may also be characterised by other analytical techniques known in the art.

Typically Form B is obtained in a hydrated form with, for example, a water content of about 9-10% w/w, for example about 9% w/w.

Form B may be crystallised from a saturated solution of the Agent in aqueous [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt (hereinafter referred to as 'Sodium Salt'). Suitably the amorphous form of the Agent is used as starting material and may be obtained, for example, as described in EPA 521471. The sodium salt may be prepared as described in WO 00/49014 and in Example 1 hereinafter.

Therefore in a further aspect of the present invention is provided a process for the manufacture of a crystalline hydrated form of a compound of formula (I) which comprises

forming crystals from a saturated solution of compound of formula (I) in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

A further aspect of the present invention provides a process for the manufacture of a crystalline hydrated form of a compound of formula (I) which comprises forming crystals from a saturated solution of the amorphous form of the compound of formula (I) in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

Saturation of the sodium salt solution with the Agent means addition of, for example the amorphous form to the sodium salt solution until the solution is saturated with respect to the amorphous form. Further amorphous form is added to maintain the saturation once crystallisation of Form B has started.

The process of the invention is conveniently carried out between 20 and 45°C, more conveniently between 30 and 45°C, even more conveniently between 37 and 43°C, and preferably at about 40°C.

Form B may also be formed by seeding an aqueous solution or slurry of the amorphous form of the Agent, or by prolonged stirring of a solution of the amorphous form.

The utility of the compound of the invention may be demonstrated by standard tests and clinical studies, including those described in EPA 521471.

According to a further feature of the invention is a method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of Form B of the Agent. The invention also relates to the use of Form B in the manufacture of a medicament for use in a disease condition.

The compound of the invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HMG CoA reductase is implicated, in the form of a conventional pharmaceutical composition. Therefore in another aspect of the invention, there is provided a pharmaceutical composition comprising Form B in admixture with a pharmaceutically acceptable carrier.

Such compositions may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the Agent may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily

solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solution or suspensions or sterile emulsions. A preferred route of administration is oral. The Agent will be administered to humans at a daily dose in, for example, the ranges set out in EPA 521471. The daily doses may be given in divided doses as necessary, the precise amount of the Agent received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further feature of the invention, there is provided a process for the manufacture of a pharmaceutical composition containing Form B as active ingredient, which comprises admixing Form B together with a pharmaceutically acceptable carrier.

It will be appreciated that the process described in WO2004/014872, for precipitation of the amorphous form of the Agent from a (substantially) aqueous solution of a different salt form, will generally lead to a proportion of residual Agent in waste solutions such as the mother liquors remaining after the precipitated Agent has been filtered off. Even a very small proportion of such residue may represent significant financial loss if the process is carried out repeatedly on a commercial manufacturing scale. Any reduction in such residue also potentially provides environmental benefits, reducing the amount of treatment that effluent requires before it can be disposed of.

We have found that this loss may be avoided by treatment of said waste solutions (such as mother liquors) such that the residue Agent may be isolated as Form B and then re-treated to form the desired amorphous form. Thus Form B has value as a processing aid for isolation of the amorphous form of the Agent. This aspect of the invention is illustrated in Example 3.

Therefore in a further aspect of the invention, there is provided a process for formation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt comprising isolation of Form B as hereinbefore defined from a solution and subsequent conversion to the amorphous form.

In a further aspect, there is provided a process for formation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt comprising mixing a solution containing [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-

dihydroxyhept-6-enoic acid] calcium salt with a slurry of Form B in water, isolation of Form B and subsequent conversion of the isolated form B to the amorphous form, wherein Form B is as hereinbefore defined.

The process for isolation of form B is conveniently carried out between 20 and 45°C, more conveniently between 30 and 45°C, even more conveniently between 37 and 43°C, and preferably at about 40°C.

The solution containing [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt is conveniently a waste solution such as a mother liquor solution from a process for formation and isolation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt from the corresponding sodium salt and calcium chloride. It will be appreciated that this waste solution will generally contain residual sodium chloride and potentially impurities arising from earlier stages in the synthetic process. The Form B isolated from this process is of high purity, for example >90% on dry weight basis, preferably >95%,more preferably >99%.

The quantity of Agent in the slurry of form B is conveniently approximately 15 mol% of that contained in the waste solution. The slurry and the waste solution are conveniently at a concentration of approximately 7mg/ml.

In a further aspect of the invention, there is provided the use of Form B (as hereinbefore defined) as a processing aid for isolation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

In a further aspect of the invention, there is provided the use of Form B (as hereinbefore defined) as a processing aid for recovery of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt from waste solutions.

In a further aspect of the invention, there is provided the use of Form B (as hereinbefore defined) as an intermediate in the amanufacture of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

Under certain circumstances the Agent may exist in a crystalline form related to Form B which generally possesses long-range order, but only limited short-range order, and which

generally has a lower water content than Form B. This form, related to Form B is hereinafter referred to as Form B-1. An XRD trace of Form B-1 is shown in Example 2.

Form B-1 is produced by the removal of water from the crystal lattice of Form B. Upon dehydration, the long-range structure of Form B is retained in Form B-1, but Form B-1 has only limited short-range order. Form B-1 may be formed by heating a sample of Form B to 60 °C or by storing a sample of Form B at 0 % Relative Humidity (RH) using equipment such as a DVS (Dynamic Vapour Sorption) instrument, for example a Surface Measurement Systems DVS_1, as described in Example 2. Form B-1 may be converted back to Form B by appropriate exposure to water, for example by slurrying in water. As illustrated in Example 2, Form B-1 demonstrates a distinct XRD pattern in comparison to that of Form B. The XRD pattern of Form B-1 may be determined by the method hereinbefore described for Form B.

Therefore in another aspect there is provided a 'dehydrated hydrate' form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.4, 7.7, 9.0 and 20.7 at 0 % RH. In a further aspect there is provided a 'dehydrated hydrate' of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.4, 9.0 and 20.7 at 0 % RH. In a further aspect there is provided a 'dehydrated hydrate' of the Agent having an X-ray powder diffraction pattern substantially as shown in Figure 2.

Exposure of Form B-1 to humidities above 0% RH allows water to re-enter the crystal lattice to a level dictated by the RH of the environment. However, water vapour does not easily reorder the structure to reproduce Form B, hence the material continues to lack short-range order and water is easily lost on lowering the relative humidity. The absorption and desorption of water may lead to small shifts in the XRD peaks.

A DRIFT spectrum of Form B-1 is included in Example 2 hereinafter. The experimental conditions were as described hereinbefore for Form B, except that the sample was gently crushed.

The invention will now be illustrated by the following Examples.

Example 1

Aqueous sodium hydroxide (8% w/w, 27.2 ml) was added to a stirred mixture of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] methylamine salt (30 g) in purified water (234 ml) at 20°C and

the mixture was stirred for 15 min. The mixture may be filtered if necessary to remove insoluble material. The mixture was concentrated under reduced pressure at <40°C until 142 ml of distillate collected. Water (90 ml) was added and the mixture again concentrated under reduced pressure at <40°C until 90ml of distillate collected. The resulting solution of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt was made up to a volume of 295 ml with water (125 ml) at 40°C and bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt (8g) (amorphous) was added. After stirring for approximately 20 hours a gel was observed. After a further 7 hours of stirring at 40°C crystallisation was observed (confirmed by optical microscopy). Further bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt (amorphous, 17g) and water (100ml) were added. The thick slurry was stirred for a further 16 hours at 40°C after which time the material appeared totally crystalline by optical microscopy. The crystalline material was cooled to 20°C, isolated, washed with water (3 x 90 ml) and dried under vaccuum at approximately 35°C to give 23g (95% yield based on 96% strength input amorphous calcium salt).

Water content 9.1% w/w

^{1}H NMR (400 MHz, DMSO-D6) δ ppm*: 1.2 (d, 3H) 1.2 (d, 3H) 1.3 (m, 1H) 1.5 (m, 1H) 2.0 (dd, 1H) 2.1 (dd, 1H) 3.4 (s, 3H) 3.5 (s, 3H) 3.8 (m, 1H) 4.2 (q, 1H) 5.5 (dd, 5.4 Hz, 1H) 6.5 (dd, 1H) 7.3 (m, 2H) 7.7 (m, 2H)

*Chemical shifts were measured in parts per million relative to tetramethylsilane. Peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

X-ray powder diffraction (XRD):

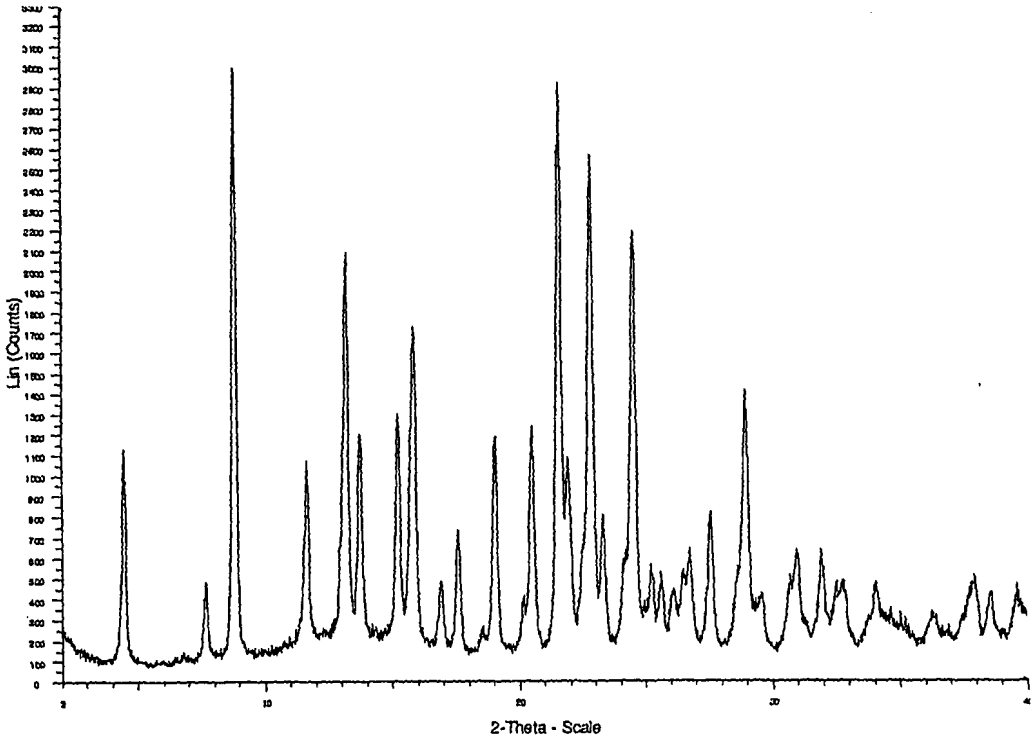
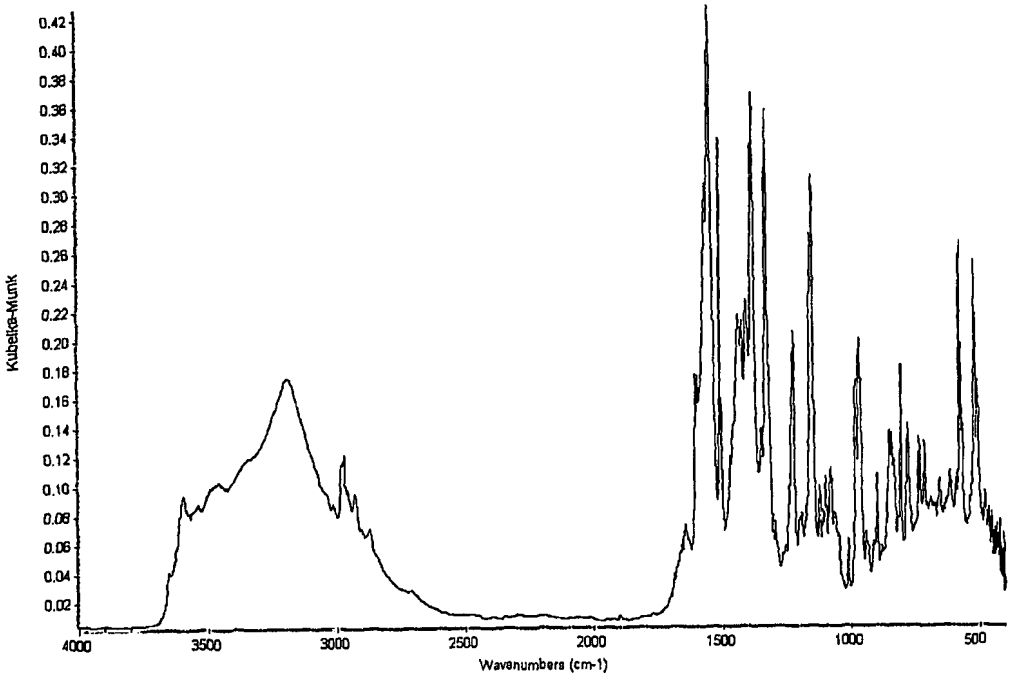


Figure 1

Peak Number	2θ	d-Spacing	Relative Intensity (>20%)
1	4.3	20.2	37.5
2	8.8	10.1	100
3	13.1	6.7	69.5
4	13.7	6.5	39.9
5	15.2	5.8	43.1
6	15.8	5.6	57.5
7	17.5	5.1	24.3
8	21.5	4.1	97.6
9	21.9	4.1	36.0
10	22.8	3.9	85.6
11	24.5	3.6	73.1
12	28.9	3.1	47.1

Form B – DRIFTS IR Spectrum



The Form B sample was crushed to a fine powder before being homogeneously mixed with KBr. Other experimental conditioans have been described hereinbefore.

Example 2

A sample of Form B (approximately 6 mg) was dispensed into a glass sample pan and suspended from the balance of an SMS Dynamic Vapour Sorption (DVS) instrument. The DVS instrument was then used to hold at 0 %RH, 30 °C, overnight (after this time period the change in sample mass was < 0.002%/min over at least an hour). The sample was then analysed immediately by XRD. The sample was exposed for 0.40 sec per 0.0357° 2θ over the range 3° to 30° 2θ in continuous scan, theta-theta mode.

The following trace (Figure 2) is an example XRD trace of a sample of Form B-1 which has been stored at 0 % RH. It will be appreciated that variations in the water content of the sample of Form B-1 will cause variations in the precise 2θ values described below, such variations in water content resulting for example by the conditions of storage of Form B-1.

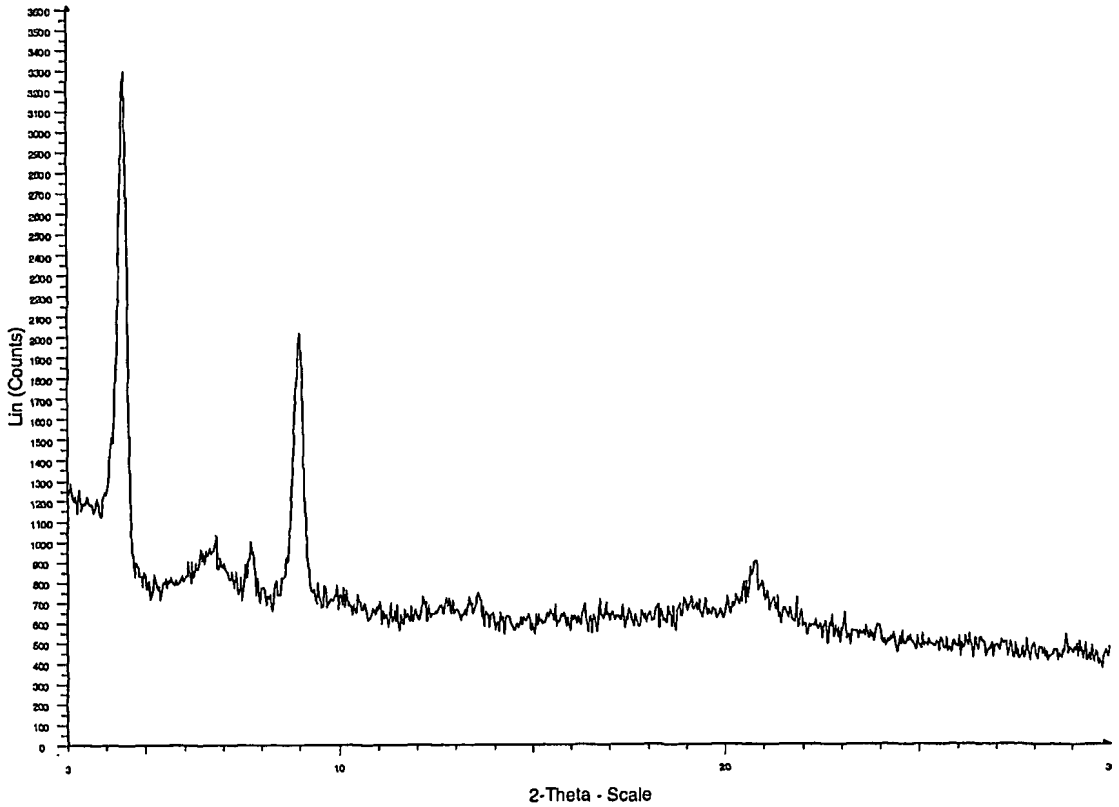
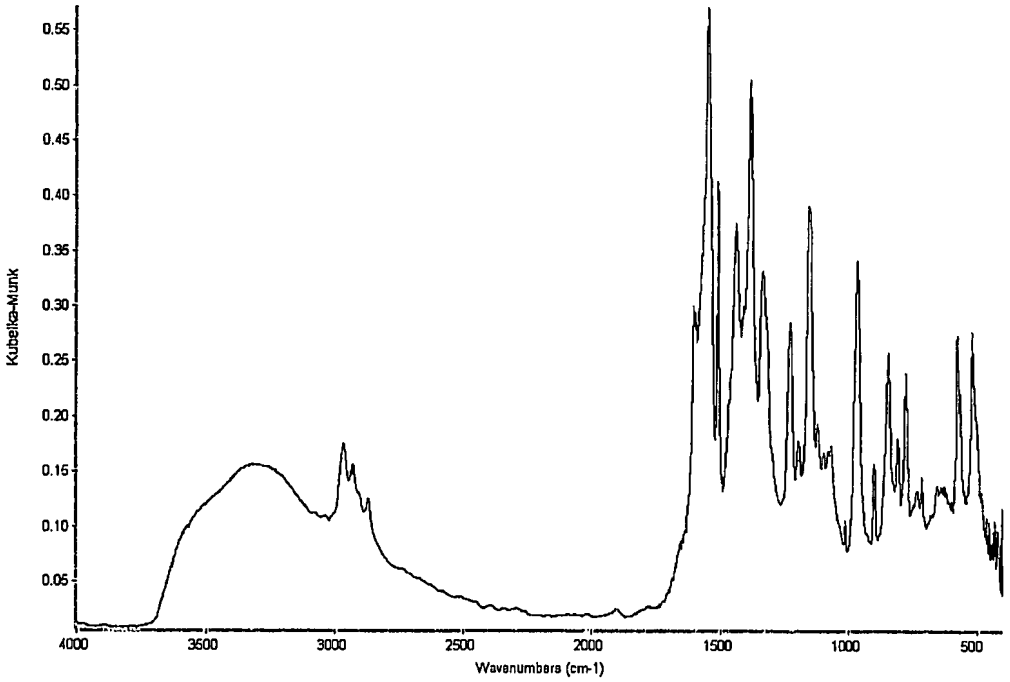


Figure 2

Peak Number	2θ	d-Spacing	Relative Intensity
1	4.4	20.0	100
2	7.7	11.4	26
3	9.0	9.9	58
4	20.7	4.3	22

Form B-1 – DRIFT IR Spectrum



The following figure (Figure 3) is a comparison of the XRD traces of Forms B and B-1:

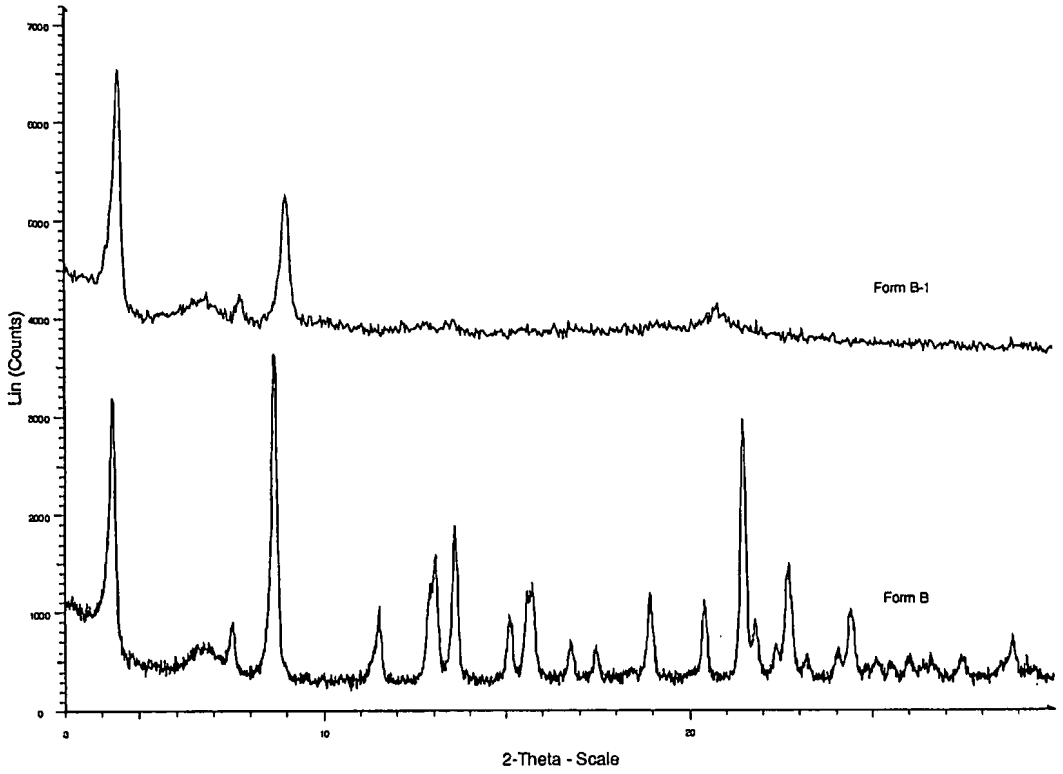


Figure 3

Example 3 : Example of Mother liquor recovery process

Bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2- [methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt mother liquors (6000ml @ approximately 7/mg/ml) and a slurry of Form B (900 ml @0.7% w/v in water) were mixed together at 40°C over 80 minutes. The slurry was then held for a further 6 hours with stirring at 40°C. The mixture was then cooled to 5°C and held at that temperature with stirring for a further 2 hours. Bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2- [methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt Form B was isolated and dried under vacuum at 22°C under nitrogen. Approximately 75% of the available Bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2- methyl(methylsulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt in the mother liquors and washes was recovered as isolated crystalline Form B.

The Form B may be converted to amorphous Agent as follows:

A suspension of crystalline Form B (17.32 g) in acetonitrile (148 ml) was treated with water (70 ml) to form a solution at 20°C. Sodium chloride (18.8 g) was added to the solution and the pH is adjusted to 2.8-3.4 at 0°C with aqueous hydrochloric acid and brine solution. The

product [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2- [methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid was extracted (or partitioned) into the acetonitrile phase then diluted with water (72 ml). The pH was adjusted to pH 10.5 with sodium hydroxide. Water was then added so that the total volume of water and sodium hydroxide added was equal to 100ml. The mixture is washed with toluene (125 ml). After removal of the acetonitrile from the aqueous phase by vacuum distillation, calcium chloride solution (3.05 g in approx 30 ml water) was added to the residue at 40°C over 20 minutes. The amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2- [methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt was isolated by filtration at 20 °C, and washed with water, before drying under vacuum to give the amorphous agent (14.2 g, 82%).

Reference Example 1

For reference purposes, Figure 4 below shows the XRD pattern for Form A, as described in WO 00/42024.

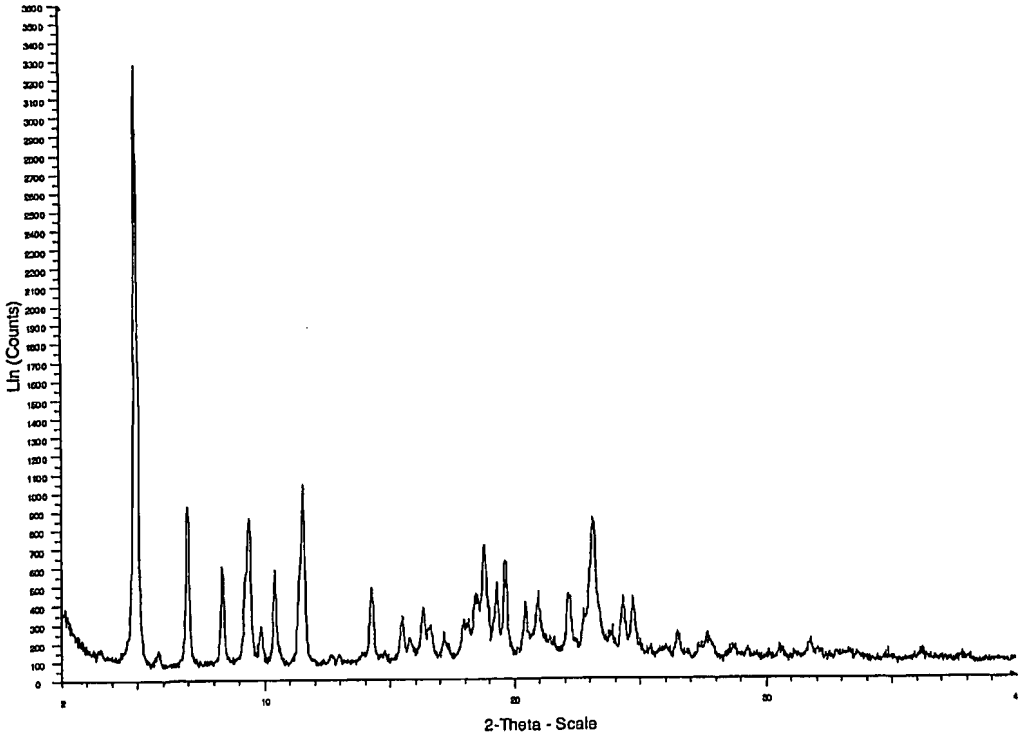
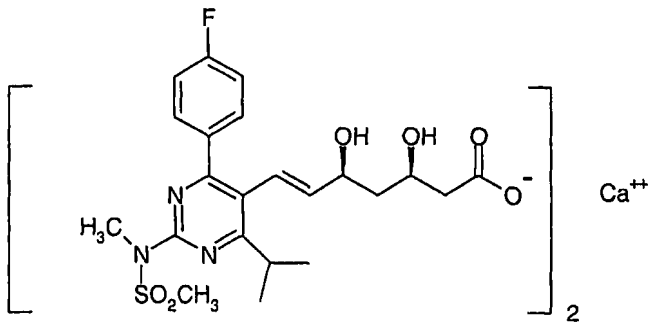


Figure 4

Claims

1. A crystalline hydrated form of the compound bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt of the formula I



I

having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 8.8, 13.1 and 21.5°.

2. A crystalline hydrated form as claimed in Claim 1 with an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 21.5, 22.8 and 28.9°.

3. A crystalline hydrated form as claimed in Claim 1 with an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 15.2, 15.8, 17.5, 21.5, 21.9, 22.8, 24.5 and 28.9°.

4. A crystalline hydrated form as claimed in Claim 1, Claim 2 or Claim 3 which contains about 9-10% water.

5. A crystalline hydrated form as claimed in Claim 1 having an X-ray powder diffraction pattern substantially as shown in Figure 1.

6. A crystalline form of a compound of formula I (as shown in Claim 1) having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.4, 7.7, 9.0 and 20.7°.

7. A crystalline form of a compound of formula I (as shown in Claim 1) having an X-ray powder diffraction pattern substantially as shown in Figure 2.

8. A pharmaceutical composition comprising a crystalline form as claimed in any one of the preceding claims, together with a pharmaceutically acceptable carrier.

9. A process for formation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt comprising isolation of a crystalline form as defined in any one of Claims 1 to 5 from a solution and subsequent conversion to the amorphous form.

10. A process as claimed in Claim 9 comprising mixing a solution containing [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with a slurry of a crystalline form as described in any one of Claims 1 to 5 in water, isolation of crystals of a crystalline form as described in any one of Claims 1 to 5 and subsequent conversion of the isolated crystals to the amorphous form.

11. A process as claimed in Claim 10 wherein the solution containing [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt is a waste solution such as a mother liquor solution from a process for formation and isolation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt from the corresponding sodium salt and calcium chloride.

12. A process as claimed in Claim 10 or Claim 11 wherein the mixing is carried out between 37 and 43°C.

13. The use of a crystalline form as claimed in any one of Claims 1 to 5 as a processing aid for isolation of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

14. The use as claimed in Claim 13 as a processing aid for recovery of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt from waste solutions.

15. The use of a crystalline form as claimed in any one of Claims 1 to 5 as an intermediate in the manufacture of amorphous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

16. A process for the manufacture of a crystalline form as claimed in any one of claims 1 to 5 which comprises forming crystals from a saturated solution of a compound of formula (I) as defined in Claim 1, in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

17. A process for the manufacture of a crystalline form as claimed in any one of claims 1 to 5 which comprises seeding an aqueous solution or slurry of a compound of formula I (as defined in Claim 1).

18. A process for the manufacture of a crystalline form as claimed in any one of claims 1 to 5 which comprises prolonged stirring of a solution of an amorphous form of a compound of formula I (as defined in Claim 1).

19. A process for the manufacture of a pharmaceutical composition as claimed in claim 8 which comprises admixing a crystalline form as defined in any one of Claims 1 to 5 together with a pharmaceutically acceptable carrier.

20. The use of a crystalline form as claimed in any one of Claims 1 to 5 in the manufacture of a medicament.

21. A method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of a crystalline form as claimed in any one of Claims 1 to 5.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/42024 A (ASTRAZENECA UK LTD ; TAYLOR NIGEL PHILLIP (GB)) 20 July 2000 (2000-07-20) cited in the application the whole document	1-21
Y,P	WO 2004/014872 A (TAYLOR NIGEL PHILIP ; HORBURY JOHN (GB); ASTRAZENECA UK LTD (GB)) 19 February 2004 (2004-02-19) cited in the application the whole document	1-21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2004	24/11/2004

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application see example 7	1-21
Y	WATANABE M ET AL: "SYNTHESIS AND BIOLOGICAL ANTIVITY OF METHANESULFONAMIDE PYRIMIDINE-AND N-METHANESULFONYL PYRROLE-SUBSTITUTED 3,5-DIHYDROXY-6-HEPTENOATES, A NOVEL SERIES OF HMG-COA REDUCTASE INHIBITORS" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 5, no. 2, 1997, pages 437-444, XP000882043 ISSN: 0968-0896 the whole document	20,21

1

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003829

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003829

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